In the autumn of 1979, I began to train for the Boston Marathon. Each day I ran from my laboratory, at the Harvard Medical School, along the Charles River and back—some fifteen miles. To increase my stamina, I began to row on a stationary machine. I soon developed a stabbing pain in my lower back. A sports orthopedist I consulted told me that I had early arthritis of the lumbar spine, probably from years of running on city pavement, and that some of the disks there were bulging from the strain of rowing.

I was told to stop all exercise, lie in bed, and begin taking high doses of aspirin. It was a wonderfully low-tech approach, and, as a physician, I appreciated its good sense. Sir John Vane, a pharmacologist in Britain, had recently elucidated how aspirin works. (He later received the Nobel Prize for it.) Trauma generates the release of substances called prostaglandins, which are responsible for the cardinal features of inflammation: pain, redness, heat, and swelling. Aspirin reduces the prostaglandins by blocking an enzyme that helps make them—an enzyme known as cyclooxygenase, or COX.

I soon learned that the reality wasn’t as elegant as the theory. Aspirin and similar nonsteroidal anti-inflammatory drugs, or NSAIDs—their trade names include Motrin and Aleve—were disappointing in their benefits and significant in their side effects: my stomach burned, my ears buzzed, I became dizzy. In desperation, I underwent back surgery. When I woke up, my legs were frozen in pain. I had bled around the spinal nerves during the operation: NSAIDs prevent blood from clotting normally, by poisoning the platelets. I was then placed on Percocet, a narcotic, which made me dopey and nauseated. For three months, I lay in bed on a rubber pad filled with ice chips to numb my back. I ended up with worsened spinal arthritis, and, like the other forty million Americans who suffer from arthritis and similar maladies, I’ve had to make do with those NSAIDs, while pondering the inadequacies of the modern medicine cabinet.

People often think of inflammation as merely an annoying symptom. But inflammation doesn’t just signal injury; it can—in a vicious cycle—perpetuate injury. That’s why disorders like arthritis can be so crippling, chronic, and hard to treat. And that’s why patients are willing to risk serious side effects for drugs that offer even a temporary respite.
Several biotech companies have plans to bring out a number of powerful drugs to treat the severest of the joint diseases, rheumatoid arthritis. So debilitating is this affliction that these treatments have been widely heralded despite their potential dangers. The drugs—including Enbrel and Avakine—may make you vulnerable to life-threatening infection and cancers such as lymphoma. In addition, the animal proteins on which some of these new treatments are based can trigger severe allergic reactions.

So the alternatives have remained grim: high-risk—and necessarily short-term—immunosuppressant therapies for people with the most disabling forms of inflammatory disease, and NSAIDs for the rest of us. But recently an industry scientist, Philip Needleman, has transformed the treatment of pain and inflammation by creating a compound that is potent in its effects yet appears to be far safer than any other known anti-inflammatory. More than ten thousand people have been tested, and none have experienced any side effects. Not only does the drug represent a quantum leap forward in the therapy of arthritis but, if some promising research is borne out, it may even play a role in preventing or treating a host of other conditions, from cancer to Alzheimer’s disease.

“So I’m cranking along, you know, studying inflammation in rabbits,” Needleman told me, in an exuberant Brooklyn accent. “And this rabbit’s kidney was exploding with prostaglandins. Where, I asked myself, was this explosion coming from?” Needleman is over six feet tall and, with his broad shoulders and fleshy face, resembles an aging linebacker. He cheerfully credits the discovery of his billion-dollar molecule to that rabbit’s kidney he was studying years ago when he was the chairman of the pharmacology department at Washington University, in St. Louis. A series of experiments involving the kidney tissue pointed to agitated white blood cells, which were recognized sources of inflammatory substances. “But then we did the T-shirt experiment!”

Needleman is one of the most eminent researchers in the study of inflammation—a member of the National Academy of Sciences and, since 1991, the chief scientist at the Monsanto Company. His lab is stocked with high-speed centrifuges, protein sequencers, and gamma counters. But a T-shirt experiment?

“You know—like, you’re with your kid, and you get a stencilled T-shirt, so you wear it across your chest,” he explained. “It’s someone or something that you believe in, that you’re willing to do anything and everything in the world to see through, to the very end. And you want to wear it on your chest—like ‘Save the Whales’—to announce to the world how committed you are.”

Needleman had bathed tissue from the inflamed rabbit kidney in a chemical that eliminated the source of ordinary prostaglandin manufacture. And yet prostaglandins were still being pumped out. What if inflamed cells had a way of manufacturing prostaglandins that was completely different from the way healthy cells did so? At this point it was merely a conjecture, but Needleman felt so confident of it that he was ready to wear it on his chest.
And the more research he did the more certain he became that there were two kinds of COX enzyme. One enzyme would provide the “housekeeper” prostaglandins—the regular, modest levels that kept our stomach, platelets, kidneys, and other tissues in working order. The second enzyme was produced only in the event of inflammation or trauma, and generated the high levels of prostaglandins that cause inflammation. If COX-1 was a garden sprinkler, COX-2 was a water cannon.

Late in 1990, at an international conference in Florence, Needleman gave an address predicting that two such forms of COX would be found, and that blocking COX-2 would selectively control inflammation without disturbing our physiology. Shortly afterward, other scientists confirmed his hypothesis and isolated the second enzyme. Now Needleman’s efforts were directed at finding a drug that could discriminate between the two enzymes. “I mobilized all the medicinal chemists at Monsanto,” he told me. “It was a once-in-a-lifetime chance.” If his faith in his hypothesis was impressive, so was his ability to convince a chemical giant that it should enlist a large portion of its pharmaceutical resources to work on a single project. In fact, he was recently named co-president of G.D. Searle, Monsanto’s pharmaceutical division.

Needleman and his expanded team attacked the problem on several fronts. By cloning the gene for COX-2, they prepared a large amount of the enzyme. Needleman had already gone on what he called a “seven-day sabbatical” to Sir John Vane’s laboratory, in England, in order to learn all the Nobel laureate’s techniques for assessing inflammation. Now he reviewed the known NSAIDs and determined which were least noxious to the stomach while still effective against inflammation. These, he reasoned, might have a much greater affinity for COX-2 than for COX-1, and their chemical structures might give a clue to why. Soon, the Monsanto group sculpted a chemical backbone that was refined into a compound, called celecoxib, that blocked COX-2 and spared COX-1. Studies of celecoxib progressed smoothly from the test tube to animals and then to man. In March, 1995, five years after Needleman floated his hypothesis in Florence, the first patient was treated with the new drug, which Monsanto has named Celebra.

For thousands of years before Needleman’s breakthrough, the medical approach to inflammation essentially amounted to variations on a theme. The ancient Egyptians employed preparations of myrtle leaves to relieve joint and other pains. Hippocrates prescribed the sap of willow bark for similar complaints and for fever. The active substance in these botanical remedies was salicylic acid. In 1897, the Bayer Company, in Germany, synthesized a more effective preparation—acetylsalicylic acid, better known as aspirin. (Cortisone, introduced with high hopes shortly after the Second World War, could not be used for chronic therapy of arthritis, because it proved to have devastating side effects.) The newer NSAIDs developed in this century are chemically distinct from aspirin but work by the same mechanism that John Vane discovered: they, too, reduce prostaglandin production by inhibiting the COX enzymes.

NSAIDs, despite their many side effects and limited potency, are some of the most heavily used drugs in the world. Indeed, they’re one of the pillars of the modern pharmaceutical industry, prescribed for everything from migraine headaches to tennis elbow. Last year, seventy-seven million prescriptions for NSAIDs were written in the
United States, and an equal quantity of these drugs was probably bought over the counter. In this country alone, they account for sales of as much as eight billion dollars a year. The cost of their side effects is more difficult to calculate, but every year some eighty thousand Americans are hospitalized, and some eight thousand die, as a consequence of them. Of course, the vast majority of people who take these pills regularly for pain don’t experience any dire medical emergencies. For many of them, including tens of millions of arthritics (whose numbers grow as the population ages), the NSAIDs present a choice between ulcers and aches. And, even at high doses, the relief afforded too often falls short of the relief required.

Rich Dillon is a fifty-three-year-old firefighter from Lincoln, Nebraska, who had long suffered from arthritis in his knees. Four years ago, the pain and swelling became so severe that he could not comfortably support the heavy bunker gear and the oxygen tank that he had to wear in order to enter a blaze and do his job. His leisure activities, too, were curtailed: more than an hour of driving caused his knees to balloon and stiffen. Dr. Arthur Weaver, a rheumatologist, diagnosed the most common form of arthritis, termed osteoarthritis. Over time, wear and tear abrades the smooth surface of the joints; the trauma generates prostaglandins; and—in that characteristic vicious cycle of inflammation—the resultant swelling of the joints only worsens the abrasion. Dr. Weaver finally prescribed Voltaren, which is a strong NSAID. “It didn’t upset my stomach,” Dillon told me. “I have a strong constitution. It just didn’t help enough.” He’s one of those arthritis patients for whom NSAIDs are limited not by their side effects but by their impotency.

About two years ago, Dillon entered a clinical trial of Celebra. “It’s been tremendous,” he says, with undisguised enthusiasm. He has had no side effects from the treatment, and has enjoyed sustained improvement in his knees. He can now do his job without pain. Still, he points out that, if he misses a single dose, within a day he notices a return of pain and reduced flexibility in his joints. The study Dillon is enrolled in ends in two years; his greatest worry is that if the drug doesn’t gain F.D.A. approval by then he may have to go back to the kind of life he had before he took Celebra.

Dillon takes only a moderate dose of Celebra: Monsanto initially proceeded cautiously in its clinical trials, seeking to establish the drug’s safety and efficacy before exploring its upper reaches. But with efficient COX-2 inhibitors clinicians may be able to address one of the most vexing scientific questions concerning arthritis: If you could reduce inflammation enough, would a joint be able to heal permanently? Should this prove to be the case, COX-2 inhibitors may represent far more than symptomatic relief. They may offer a means of modifying the underlying disease itself. Potent inhibition of COX-2 also opens up the possibility that noxious and addictive narcotics, like codeine and Percocet, could be superseded—and there’s been support for this in clinical trials of Celebra for dental pain. (It’s noteworthy that American Home Products, which recently announced plans to merge with Monsanto, makes Advil, an ibuprofen-based pain reliever that Celebra may ultimately render obsolete.)

Excitement about COX-2 inhibitors is growing even among cancer researchers. Several studies published during the past decade have indicated that patients taking NSAIDs have a fifty-per-cent-lower incidence of colon cancer. But only recently have scientists figured
out why this might be. Most colon cancer is believed to arise from two sequential mutations. The primary mutation causes levels of COX-2 in the cells to soar, which results in excessive growths called polyps. A second mutation can then cause a polyp to become cancerous. It stands to reason that inhibiting COX-2 would block the first step of the process, and there’s now evidence of this in studies of mice specially bred to have the primary mutation. These mice are prone to develop precancerous polyps, but when they’re given Celebra, such polyps never develop and cancer never gets started. Clinical trials of Celebra as a cancer preventive are already under way in people who have multiple colonic polyps and are at high risk for colon cancer.

Philip Needleman thinks the results of these trials will mirror what has been seen in the mice. He readily admits that mice are not men, but there is now hard science to explain the reported link between NSAIDs and a lowered incidence of colon cancer. What’s more, COX-2 may play a role in other kinds of cancer as well. Researchers are hastening to analyze tumor specimens for the enzyme, and there are indications that breast cancer is also promoted by COX-2.

Alzheimer’s disease is another debilitating malady for which COX-2 blockers are being tested. When I asked Needleman why blocking COX-2 might help, he replied, “Ver veyst?”—Yiddish for “Who knows?”—and added, “Ask your neighbor Cliff Saper.”

Clifford Saper is a professor of neuroscience at Harvard and a prominent figure in the biology and treatment of Alzheimer’s disease. Saper told me that there have been fourteen published studies on NSAIDs and Alzheimer’s disease which showed a significant decrease in the progression of the disease when NSAIDs are used. Saper had been tracking the research, and he and Needleman talked about it. “At the time, everyone was focussed on arthritis,” Saper said. “But when Phil is struck by an idea nothing can stop him. He’s like a force of nature.”

How might a COXx-2 inhibitor be helpful in treating Alzheimer’s? Saper points out that when a neuron in the brain is damaged an inflammatory reaction occurs, but that—as happens with arthritis—this inflammation can itself cause more damage. Celebra, he said, promises to “break open the vicious cycle of inflammation in Alzheimer’s.” A national study of Celebra is under way, with more than three hundred patients who have mild to moderate Alzheimer’s disease. Saper says he expects to find that the drug slows the rate of cognitive deterioration by at least fifty per cent.

The potential market for COX-2 inhibitors is enormous. Analysts have projected sales of up to five billion dollars a year in the United States. (Prozac, by comparison, has sales of two billion dollars.) Monsanto is seeking initial F.D.A. approval only for the treatment of arthritis. But Celebra is likely to have considerable “off-label use”—as physicians use it to replace narcotics for relief of moderate pain and, in particular, for analgesia before and after operations, when conventional NSAIDs can cause uncontrolled bleeding. And if Celebra should eventually prove to be a safe way of preventing colon cancer and slowing Alzheimer’s disease, the sales would be stratospheric. The total market could easily exceed ten billion dollars yearly in the United States alone.
Given these figures, the arrival of Celebra, which represents not merely a new drug but a new category of drugs, has invited fierce competition. Merck, a formidable opponent, has already completed advanced clinical trials of a COX-2 inhibitor of its own, called Vioxx. The development of both Vioxx and Celebra required screening tens of thousands of compounds in tedious test-tube assays. A second generation of COX-2 inhibitors will take advantage of recent developments in computerized drug design. Computers can now assess how different chemical structures fit into the nooks and crannies of the COX-2 molecule. It turns out that there are subtle but important differences between the surfaces of COX-1 and COX-2: the latter enzyme has a so-called side pocket, into which a selective blocker like Celebra fits snugly. In the meantime, Needleman has confirmed that Monsanto’s computer analysis of the COX-2 molecule has already yielded a “son of Celebra,” or second-generation inhibitor. Celebra has a thousandfold propensity to block COX-2 over COX-1; the new compound’s selectivity is forty-two-thousandfold.

But could there be a third COX enzyme? Sir John Vane has recently speculated that there might be such an enzyme, which could mediate pain and fever rather than inflammation. “I look every day at new gene sequences in the database,” Needleman told me, referring to the growing repository of DNA codes that have been deciphered. He is seeking similarities between recently discovered genes of unknown function and the known gene sequences of COX-1 and COX-2. So far, he hasn’t seen any evidence of a COX-3, nor has anyone else, as far as we know. But when the stakes are this high, scientists and their companies are constantly in a state of restless vigilance. “What you don’t know worries you,” Needleman admits.

“If our luck holds, in less than two years I won’t have to do this to you,” Lee Simon said as he injected my elbow with cortisone; I’d banged it a couple of weeks earlier and had developed bursitis.

Dr. Simon, a colleague of mine at Harvard, works on innovative treatments for arthritis. He helped design the Celebra trials, and was one of the organizers of the First International Workshop on COX-2, which was held in New Orleans this past September. He’s known in the field for having a sharply critical attitude toward most of the new therapies being touted for inflammation. Over the two decades of his career, he has seen many false starts and has developed an ingrained wariness. So I was startled by his assessment of the new COX-2 inhibitor.

“Celebra is incredible,” he said, and went on to point out that more than ten thousand patients have received the drug—many, like Rich Dillon, for more than a year—and no side effects have been observed. “None,” he repeated. He knew this because of the lengths to which he and others have gone to look for toxicity—even peering right into people’s stomachs via endoscopy. Take a handful of aspirin, and you’ll start to hear ringing in your ears, but in studies of animals that are much more sensitive to COX inhibition than people are, researchers had to administer an amount of Celebra that was at least a hundred times as great as the therapeutic dose before any side effects began to appear. Twenty per cent of a group of people taking naproxen (the active ingredient of Aleve) had developed gastric ulcers after only one week of treatment; none of those taking Celebra had. Investigators had also isolated platelets from Celebra-treated patients.
and found the cells to be unaffected. The clinical trials in dental pain, rheumatoid arthritis, and osteoarthritis had proved that Celebra significantly and powerfully alleviates pain and, in arthritis, also improves the range of joint motion.

“It seems too good to be true,” I told Lee Simon. Clinical investigators always have to guard against euphoria. It’s easy to be blinded by the love of your hypothesis, to scant the counterevidence the way a parent overlooks the misbehavior of a child. Simon conceded that the clinical experience is still limited in time: no one has taken a COX-2 inhibitor every day for decades. But so far all the signs are good—and for people like me they are more than good. I imagine myself, in the year 2000, popping a pill, comfortably bending down to tighten the laces of my sneakers, and beginning the twenty-six miles from Hopkinton to Boston.